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Effect of diet and gut environment on the gastrointestinal formation of *N*-nitroso compounds: A review

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A B S T R A C T

Diet is associated with the development of cancer in the gastrointestinal (GI) tract, because dietary nitrate and nitrite are the main nitrosating agents that are responsible for the formation of carcinogenic *N*-nitroso compounds (NOCs) when nitrosatable substrates, such as amine and amide, are present in the GI tract. However, whether the nitroso compounds become beneficial *S*-nitroso compounds or carcinogenic NOCs might depend on dietary and environmental factors including food stuffs, gastric acidity, microbial flora, and the mean transit time of digesta. This review focused on GI NOC formation and environmental risk factors affecting its formation to provide appropriate nutritional strategies to prevent the development of GI cancer.

Contents

1. Introduction

[1]Most gastrointestinal (GI) cancers are sporadic and arise in individuals with environmental rather than hereditary risk factors. Among the environmental factors influencing the risk of developing GI cancer, diet is the strongest contributor [88]. Western diets, which are typified by high fat, high meat, and low fiber content, are associated with an increased risk of colorectal cancers. A high-fat diet increases bile acid secretion that is transformed by colonic microbiota into secondary bile acid with genotoxic properties of DNA damage due to reactive oxygen and nitrogen species [7,87]. On the other hand, a high fiber diet leads to undigested carbohydrate residue in the colon, which is fermented into short chain fatty acids due to obligated anaerobic bacteria residing in the lower intestine. These bacteria provide not only a major energy-yielding substrate for epithelial cells, but also beneficial intestinal

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[1] Abbreviations: GI: gastrointestinal; NOC: *N*-nitroso compounds; IBD: inflammatory bowel disease; pO_2: partial oxygen pressure.

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environments that suppress inflammatory responses and protect against cancer development [33,52]. On the other hand, protein-rich diets provide inflammatory and toxic nitrogenous metabolites such as phenols, indoles, ammonia, and amines that are provided by microbial fermentation of undigested protein residues [38]. These nitrogenous metabolites include *N*-nitroso compounds (NOCs), such as nitrosamine and nitrosamide, which are well-known potential carcinogens formed by the reaction of nitrosating agents, such as nitrite and secondary amines and amides, and are a prominent risk factor of GI cancer. They are potent alkylating agents that induce G-C to A-T transitions at the second base of codon 12 or 13 of the K-*ras* gene [11] in the epithelial cells, and cause cancer development in the GI tract.

Many studies of mice and rats that were given nitrite in their food and drinking water showed increased incidences of benign and malignant tumors at many organ sites [29,54], providing sufficient evidence of the GI carcinogenicity of nitrite [30]. On the other hand, nitrate itself is relatively non-toxic below maximum levels in the context of carcinogenicity. However, the catalytic intermediates of nitrate, such as N_2O_3 and NO^+, are important in NOC formation and carcinogenesis. Their presence has led to the present restrictions on nitrate in drinking water and the current acceptable daily intake recommendations of nitrate and nitrite issued by the European Food Safety Authority and the World Health Organization (WHO) [2,83]. According to the Joint Food and Agriculture Organization/WHO Expert Committee on Food Additives in 2008, epidemiological studies showed no consistently increased risk for cancer with increasing consumption of nitrate. FESA also stated in its 2008 report that epidemiological studies do not suggest that nitrate intake from diet or drinking water is associated with increased cancer risk [2]. In epidemiological studies on humans, although chronic exposure to nitrate in food and drinking water was reported to be associated with an increased risk of colon cancer, its risk was limited to those with low vitamin C intake and high meat intake [24,25], suggesting that its risk is likely to be affected by a combination of food and dietary nitrate.

Dietary nitrate and nitrite usually come from vegetables and fruits, and are experimentally and epidemiologically demonstrated to be protective against cancer development because of the many nitrosation inhibitors that are included in these foods [13]. In addition, saliva is a major dietary source of nitrite, and it is always swallowed with fully masticated foods. Around 93% of the total daily ingestion of nitrite is from saliva [4,14], because the enterosalivary route provides nitrite by recycling 25% of the dietary nitrate in the oral cavity [64], where salivary nitrate is reduced to nitrite by oral bacteria. It then enters the stomach. If this nitrite is a main contributor to NOC formation and subsequent cancer promotion, it is necessary to keep spitting to expel the saliva. However, clinically, this is not necessarily the case. This is because NOC formation in the GI tract is multifacetedly affected by a combination of many environmental factors including a variety of nitrosating agents, food stuffs, gastric acidity, and intestinal microbial flora. Therefore, a question arises as to what drives dietary nitrate toward the promoter or protector of GI tract cancer. This review focused on carcinogenic NOC formation and the environmental risk factors affecting its formation, and provided an appropriate scientific approach to nutritional strategies to prevent GI tract cancer.

2. *N*-nitroso compounds and gastrointestinal cancer

Dietary intake of preformed NOCs, which are included in cured and processed meat and beer, is positively associated with colorectal cancer [55], but endogenous NOCs can be formed more often wherever both nitrosating agents and nitrosatable substrates coexist in the body [38]. This formation in the GI tract is affected by many factors including diet such as red meat, with or without dietary antioxidants such as polyphenol and ascorbic acid [59], stomach acidity [32], medication with antacids such as a proton pump inhibitor [59], bacterial flora in the gut, and the mean transit time of dietary residue through the colon [39] (Table 1). Below, we will propose three mechanisms for this process: chemical (acid-catalyzed), bacterial, and inflammatory NOC formations, and discuss in detail the underlying factors affecting NOC formation in the GI tract in the esophagus, stomach, and colon.

3. *N*-nitroso compounds in the esophagus and stomach

The stomach might be a catalytic organ that drives dietary nitrate and nitrite toward beneficial or carcinogenic NO-related compounds. In general, dietary nitrite, the major nitrosating agent derived from diets and/or reduction of salivary nitrate due to oral bacteria, is catalyzed in the acidic stomach to generate NO-related compounds, such as *S*-nitroso, N-nitroso, *O*-nitroso compounds, and NO [28,67]. In the acidic stomach, nitrite equilibrates

Table 1
Diets, nutrients and medicines affecting NOC (ATNC) formation in the GI tract.

Diets, nutrients, drugs	Fecal (gastric) NOC levels	Species	Mechanisms	Ref.
nitrate in drinking water (300 mg nitrate/day)	increases NOC levels	human	nitrosating donor	[71]
dietary preformed NOC (hot dog, cured meat)	increases NOC levels	human	intake of NOC	[55,59]
red meat	increases NOC levels	human	heme-mediated nitrosation	Table 2
soy	decreases ATNC enhanced with red meat diet	human	reduced intestinal transit time	[40]
ascorbic acid	decreases ATNC enhanced with $NaNO_2$ in drinking water	human	antioxidant, inhibitory effect on nitrosation	[59]
green tea or black tea drinking after meal	decreases NOC enhanced with meal	human	possibly related to polyphenol content in tea	[92]
vegetables	decreases ATNC enhanced by 15 days' red meat diet	human	antioxidant, inhibitory effect on nitrosation	[22]
cimetidine (H_2 receptor antagonist)	increases NOC levels (in gastric juice)	human	increase in nitrite and intragastric bacterial overgrowth	[69]
omeprazole (proton pump inhibitor)	decreases ATNC enhanced with $NaNO_2$ in drinking water	human	decrease in acid-catalyzed nitrosation	[59]
high protein low carbohydrate and fiber diet(weight- loss diet)	increases NOC levels	human	increase in protein fermentation and decrease in carbohydrate fermentation	[74]
calcium carbonate	decreases ATNC enhanced with cured meat	human, rat	bind to dietary heme iron and suppress its toxicity	[65]
α-tocopherol		rat	antioxidant, inhibitory effect on nitrosation	

NOC: *N*-nitrosocompound, ATNC: apparent total *N*-nitrosocompound, GI: gastrointestinal.

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